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THE INFLUENCE OF PRODUCTS OF PATHOLOGIC METABOLISM ON THE DEVELOPING TELEOST OVUM.

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In his recent work on pathological human ova, after careful sifting of anatomical evidence, Mall¹ arrives at the conclusion that the failure of large numbers of ova to develop normally is to be traced to diseases of the uterus. According to his view, which is supported by obstetrical and gynecological data, diseases of the uterus are the primary cause of the faulty implantation of the ovum. This in turn makes proper nutrition of the developing embryo impossible thus leading to various degrees of malformations by arresting development. The deformed embryo is eventually aborted after it has exhausted its inadequate means of subsistence in the uterus. Full-term monsters would be born from such deformed embryos if they were not hindered in their further development by starvation. According to this theory, therefore, an apparently healthy ovum discharged into a diseased uterus fails to develop normally owing to its defective implantation.

Mall studied largely pathological ova of the first two months and the interpretation of the numerous cases described by him seems justified. Practically all pathological ova of the early months studied by him as well as by other investigators, exhibited the condition of faulty implantation, so that it is not unwarranted to regard this condition as the direct cause of monstrous development.

A consideration of some instances of arrested, defective or even monstrous development found after full-term birth would suggest, however, that there must be also some other factors

¹ Mall, F. P., "A Study of the Causes Underlying the Origin of Human Monsters." *Journ. of Morphology*, Vol. XIX., 1908; "The Pathology of the Human Ovum" in Keibel-Mall "Handbook of Human Embryology," 1910.

which primarily interfere with normal development. Such defects as rudimentary development of one or both eyes, congenital absence of both arms, hydrocephalus, possibly also cases of congenital deafness, to mention only a few that are well known to occur, can, in the writer's opinion, hardly be traced to defective implantation. The results of investigations in experimental teratology by Panum,¹ Dareste² and more recently by Stockard³ and Bardeen⁴ would seem to suggest that some physico-chemical factors may be at work in a great number of cases of pathological development. These factors may in some instances be the primary cause of terata, while in other cases they may be only secondary contributing causes.

The experimental teratologists subjected developing ova in very early stages to changes in the physico-chemical nature of the environment and found that various monstrosities could be produced under these conditions. It was impossible, however, for them to control the results of experimentation, as they could not predict the type of monster which would result from the employment of the same factors. The experiments of Stockard, where a more or less definite monstrosity—cyclopia or monophthalmia—appeared with considerable certainty in a large percentage of embryos developing in magnesium chloride or alcohol solutions, mark a distinct progress in this field of inquiry, because they paved the way towards experimental control of monstrosities occurring in nature.

To the writer Stockard's work suggested the possibility that the monstrosities met with in higher animals and man may to a certain extent be due to the influence of injurious substances found in the circulation under pathological conditions. While this hypothesis could not be applied to bacterial toxins on account of insufficient knowledge, it seemed that some substances thrown into the circulation in various metabolic diseases may be re-

¹ Panum, "Entstehung der Missbildungen," 1860.

² Dareste, "Recherches sur la production de monstrosities," Paris, 1891.

³ Stockard, C. R., "The Artificial Production of a Single Median Cyclopean Eye in the Fish Embryo by Means of Seawater Solutions of Magnesium Chlorid," *Arch. f. Entwmech.*, Vol. XXII., 1907; "The Influence of Alcohol and Other Anæsthetics on Embryonic Development," *Am. Jour. of Anat.*, Vol. X., 1910.

⁴ Bardeen, C. R., *Jour. of Experimental Zool.*, 1907; *Am. Jour. of Anat.*, Vol. XI.

sponsible for pathological development. Thus the etiology of defective or monstrous development would be traced to the pathological metabolism of the mother or possibly even of the father. For, as Bardeen¹ has shown, a normal, healthy ovum of the toad, if fertilized with sperm which had been injured by exposure to the action of X-rays, will give rise to a deformed embryo.

With this idea in mind the writer conducted during the summer of 1914 experiments on eggs of *Fundulus heteroclitus*. The eggs of this fish are easily obtained at Woods Hole and are excellent material for experimentation. The investigations on the fish eggs are of a preliminary character, and were undertaken to ascertain the influence of some toxic substances occurring in pathological metabolism on the developing egg.

The number of these substances being rather large while the spawning season is limited to a few weeks, it was impossible to try more than a few of the chemicals. Urea, butyric acid, lactic acid, sodium glycocholate, acetone and ammonium hydroxide were tried as to their effect on the development of fertilized eggs. Definite results were so far obtained only with butyric acid and acetone.

Ten c.c. of a 1/12-1/14 molecular solution in 50 c.c. of sea water was found to give the greatest number of monsters when butyric acid was used. The eggs were submitted to the action of this solution for 20 hours after they had reached the eight-cell or sixteen-cell stage, *i. e.*, 3 to 3½ hours after fertilization. While under this procedure numerous monstrosities were at first obtained, the method failed almost completely in later experiments. I therefore employed developing eggs in the first stages of division (2- and 4-cell stages) when many monstrosities were produced even after a sojourn of thirty hours in the butyric acid solution. But it seems to me that the reason why the method failed with the eggs in more advanced cleavage stages was that the time of exposure was too long, as very many eggs were dead by the end of that treatment, and that with an exposure of 10 or 15 hours better results would have been obtained.

There is, however, as important difference in the effect which

¹ Bardeen, C. R., *Jour. of Experimental Zool.*, 1907; *Am. Jour. of Anat.*, Vol. XI.

this toxic substance has upon developing eggs in the first and second or in the third and fourth divisions. In the former case anterior hemiembryos, dwarf embryos with deformities of the eyes or of the otic vesicle, and malformations of the most extreme kind were predominant, while in the latter deformities of the eye such as cyclopia and monophthalmia, etc., were mostly observed. In either case, however, there were very few embryos in which only the nervous system was affected. In most of the deformed embryos all organ systems were more or less involved in the malformation.

Similar results were obtained with acetone in sea water, varying in concentration from 20–50 c.c. of a molecular solution in 50 c.c. of sea water. In this mixture the eggs remained from 24–72 hours from the eight-cell or sixteen-cell stage. In every case great numbers¹ of monsters similar to those already mentioned were produced.

The monstrosities in both series of experiments with butyric acid and acetone being essentially alike it will not be necessary to describe separately the deformities produced by each.

Cyclopia and asymmetric monophthalmia were found to occur rather abundantly. There were also some cases of asymmetric monophthalmia in which an open orbit was found on the side lacking the eye. It is of some interest to note in this connection that the eyeless orbit in such cases is usually closed on the outside by periorbital tissues. The anatomy of the head of such embryos may probably reveal some interesting conditions. Other cases of asymmetric monophthalmia were found in which an apparently free eye had developed on the yolk-sac at a considerable distance from the embryo. Probably the most striking of the results obtained in this investigation were some eggs in which nothing could be observed but an eye. In only one case this eye seemed to be perfectly developed, while the other solitary eyes had "coloboma"-defects, the fissure of the chorioid still being patent. Only a few (five or six) of these malformations are recorded, but in spite of their rare occurrence they are very significant from the standpoint of experimental embryology. At the

¹ No attempt was made to ascertain the percentage of the deformities found in these experiments, this part of the work being deferred to later investigation.

present time it is, obviously, impossible to account for the occurrence of these remarkable cases. However, it is hoped that an anatomical investigation of early stages in the development of eggs subjected to the influence of the environmental modifications used in these experiments, may give at least a clue as to what may have happened in the development of these eggs. Practically all other known deformities of the eye such as total blindness, or presence of lenses only, or presence of supernumerary lenses were frequently found.

To the student of the physiology of development the occurrence in these experiments of large numbers of anterior hemiembryos which seem to be closely analogous to those obtained by mechanical means by Roux,¹ Endres,² Morgan³ and K. Ziegler⁴ will be of special interest. As will be pointed out soon the formation of the hemiembryos in these experiments may also possibly be due to similar factors.

A great number of embryos were hydrocephalic and so far as could be determined it is reasonable to expect that an anatomical investigation may reveal in some deformed embryos oedematous conditions, also herniae and other mechanical obstructions which played a part in their formation.

Striking abnormalities of the heart and blood-vascular system were found in all malformed embryos with the exception of those which showed only median cyclopia. Some were entirely devoid of the heart, while other possessed an exceedingly delicate tube in its place which was practically straight and of about the size of the intestinal blood vessels in a normal embryo of a corresponding stage. The rate of the heart beat varies with the degree of the abnormality of the organ, and is, as a rule, very slow in all monstrous embryos. The range of variation in the development of the blood vessels is very wide. There may be merely blood islands scattered on the yolk-sac, rudimentary, imperfectly connected, or in some instances more or less normal vessels.

¹ Roux, W., "Gesammelte Abhandlungen zur Entwicklungsmechanik der Organismen," II., 1895.

² Endres, H., "Anstichversuche an Froscheiern," *Sitzber. d. zool.-bot. Sektion d. schlesischen Ges. f. vaterländische Kultur*, 1894.

³ Morgan, T. H., "The Formation of the Embryo of the Frog," *Anat. Anz.*, 1894.

⁴ Ziegler, K., "Zur Postgenerationsfrage," *Anatomische Hefte*, Vol. LXVI., 1902.

Twins were found only in a few cases and only once were true "Siamese" twins observed. They were much deformed, had one common heart and only vestigial eyes. Several eggs were recorded, in which an anterior duplicity had developed. In one of these latter cases the components of the duplicity were totally blind, hydrocephalic, their hearts were very delicate, the blood vessels rudimentary and the yolk-sac was covered with dense networks of richly pigmented blood islands.

These monstrous embryos hatch only very rarely, most of them dying after the development has reached the stage in which the remnant of the yolk-sac is in the normal embryo converted into the anterior body wall. As far as could be determined from the embryos in toto it is the enormously large (œdematous?) pericardia that mechanically obstruct the formation of the ventral body wall. The correctness of this interpretation will be tested by microscopic sections of these embryos.

The mechanism of the formation of the described monsters can at this time not even be definitely suggested. The observation was made that the yolk-sac in all extremely malformed embryos shows a marked decrease in size as compared with that of normal eggs of the corresponding stage of development. The greater the degree of injury inflicted on the embryo the smaller the yolk-sac. It is not impossible that the chemicals used in these experiments indirectly bring about this decrease in the size of the yolk-sac. For it was noticed that the chemicals used in these experiments softened the egg-membrane considerably, a fact which suggests an increase in the permeability of the egg. Owing to both increased permeability of the germ-disc cells and to internal osmotic pressure of the yolk-sac, an escape of substance from the yolk-sac might have been caused, which, being forced out at different points of the yolk-sac, might have fragmented the germ-disc. Many eggs were observed in which this fragmentation of the germ-disc was very evident. Some parts of this ruptured germ-disc may be so badly damaged as not to be able to develop further, while the remaining fragments, even if they are very small, may still give rise to various monsters, hemiembryos, dwarfs or even to a solitary eye. Or possibly the decrease in size of the yolk-sac of malformed ova may point to

elimination of both yolk-sac and germ substance as an effect of the solvent action of the chemicals to which the eggs were exposed. Whatever the mechanism involved in the production of the recorded pathological ova may be, at the present time, it can hardly be more than conjectured. It will be the object of future investigations to find a satisfactory answer to this open question.

There seems to be a close similarity between these cases where parts of the germ-disc are apparently lost through elimination of some kind and the production of hemiembryos by mechanically injuring one of the blastomeres of the developing frog's egg, as described by Roux, Morgan and other investigators.

The writer intends to continue this work on the teleost eggs as well as on the amphibian and hen's eggs. He also hopes that he may in the near future secure adequate facilities for carrying on experiments on the influence of the toxic substances of pathological metabolism on the development of the mammalian embryo. The plan of this work would be to mate animals in which metabolic disturbances had been produced experimentally.

A complete description and analysis of the results obtained in the investigation reported here will be published at an early date.

The writer takes pleasure in acknowledging his indebtedness to Professor C. R. Stockard of Cornell University Medical College with whom he on several occasions had discussed some phases of the work, and from whom he has received valuable suggestions regarding preservation of material.

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September 3, 1914.